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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,570	09/27/2004	Julio Cesar Aguilar Rubido	976-18 PCT/US	9315

23869 7590 11/02/2007

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EXAMINER	
PENG, BO	
ART UNIT	**PAPER NUMBER**
1648	

MAIL DATE	DELIVERY MODE
11/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,570	RUBIDO ET AL.	
	Examiner	Art Unit	
	Bo Peng	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *4-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 13-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This Office Action is in response to the amendment filed August 6, 2007. Claims 1-20 are pending. Claim 1 is amended. Claims 4-12 were withdrawn as non-elected. Claims 1-3 and 13-20 are under consideration in this Office action. Claim 13 reads on Applicant's elected species, wherein the multivalent vaccine formulation comprising HBV surface antigen (HBsAg) with tetanus toxoid antigen (TT), diphtheria toxoid antigen (DT), *Bordetella pertussis* (Bp), and anti-*Haemophilus influenzae* type b (Hib),

35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. The rejection of Claims 1-3 and 13-20 under 35 U.S.C. 103(a), as being obvious over Schmitt (2000), Alpar (2001) and Isaka (2001), all in view of EP 0864649A2 (1998), **is withdrawn** in view of the amendment.

4. Following is a new ground of rejection necessitated by Applicant's amendment.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-3 and 13-20 are rejected under 35 U.S.C. 103(a) as being obviousness over Schmitt (2000), Alpar (2001) and Isaka (2001), all in view of EP 0864649A2 (1998) and Berstad AK et al Vaccine. 2000 Mar 17;18(18):1910-9).

7. Claims 1-3 and 13-20 are directed to a multivalent vaccine formulation for nasal administration comprising HBsAg produced by *Pichia pastoris* and a number of 1 to 5 other antigens, wherein the HBsAg is a mucosal immunoenhancer of soluble antigens, *Bordetella pertussis* **whole-cell** and inactivated poliovirus, wherein the other antigens are tetanus toxoid antigen (TT), diphtheria toxoid antigen (DT), a conjugate protein-polysaccharide corresponding to a vaccine antigen anti-*Haemophilus influenzae* type b (Hib), a conjugate protein-polysaccharide corresponding to polysaccharide C of *Neisseria meningitides* conjugated to a carrier protein, a conjugate protein-polysaccharide wherein the polysaccharide part corresponds to a vaccine polysaccharide of *Pneumococcus pneumoniae*, inactivated microorganisms, the bacterin *Bordetella pertussis*(Bp), inactivated virus, attenuated virus, or mixtures of them and other antigenic types, which receive an immunoenhancing effect because of their co-administration with HBsAg, wherein the antigens are TT, DT, Hib and Bp, wherein the volume of the final formulation is ranging from 50 microliters to 2 milliliters, wherein the amount of antigen to be inoculated range from 0.1 micrograms to 2 mg, wherein the antigen mixture is

dissolved in PBS, saline solution, water for injection or in any buffer solution used in medical practice or that allows the stability of the antigens.

8. Schmitt teaches multivalent vaccine formulations comprising HBsAg + DTaP+Hib + inactivated poliovirus given as either separate or mixed injection. The multivalent vaccines have been tested in a total of 359 infants of 2, 3 and 4 months of age. Schmitt teaches that the multivalent formulations are safe, immunogenic and well tolerated (Whole document).

9. Schmitt does not explicitly teach using HBsAg produced by *Pichia pastoris*, nor a whole-cell *Bordetella pertussis* vaccine.

10. Alpar teaches intranasal formulations of TT/DT vaccines against tetanus and diphtherias. Alpar teaches a verity of adjuvants for TT and DT vaccines to enhance immunogenicity of TT and DT following nasal delivery (2.3-2.5, pp 190-196). All these results show that TT and DT can be used for nasal immunization along or with mucosal adjuvants. As compared with solutions of TT/DT in PBS, the adjuvants used in the studies can successfully facilitate an intranasal vaccination of TT/DT (Figure 9-10 and pp.191-193).

11. Isaka (2001) teaches intranasal administration of HBsAg (1ug-5ug) along or with rCTB as adjuvant in a mice model. Isaka teaches that both HBsAg vaccine formulations are safe and immunogenic, and rCTB is an effective mucosal adjuvant to enhance the immunogenicity of HBsAg.

12. EP0864649 teaches recombinant HBsAg vaccine produced in *Pichia pastoris* (see Description). EP0864649 teaches that recombinant HBsAg form into particles of 22 nm, in *Pichia pastoris*, which confers superior immunogenic characteristics (p. 3). EP0864649 also teaches that HBsAg vaccine produced in *Pichia pastoris* is more immunogenic than

commercially available HBsAg vaccine (from Smith & Kline) (Example 6).

13. Berstad et al teaches a nasal whole-cell *Bordetella pertussis* vaccine (whole document). Berstad teaches that each dose consisting of 250 ug of a whole-cell *Bordetella pertussis*, was given intranasally four times at weekly intervals to six adult volunteers. All vaccinees responded with increases in nasal fluid IgA antibodies to *Bordetella pertussis* whole-cell antigen, inducing specific systemic and cross-reactive mucosal antibody responses (Abstract).

14. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine HBsAg produced by *Pichia pastoris* with TT, DT with or without Hib for intranasal immunization, as taught by Schmitt, Alpar and Isaka. One skilled in the art would have been motivated to do so in order to receive the expected benefit of mucosal immunization of multivalent vaccines, eliciting protection against several diseases at the same time, as suggested and taught by Schmitt, Alpar and Isaka. There would have been a reasonable expectation of success, given the knowledge that multivalent vaccine formulations of HBsAg with TT, DT and Hib have been proven to be safe and effective in protecting infants from diseases, as taught by Schmitt, given the knowledge that HBsAg, or TT/DT are safe for intranasal administration, as taught by Alpar and Isaka, given the knowledge that HBsAg produced by *Pichia pastoris* is more immunogenic than some commercially available HBsAg vaccine, as taught by EP0864649, and also given the knowledge that a nasal *Bordetella pertussis* whole-cell antigen can induce specific systemic and cross-reactive mucosal antibody responses in human, as taught by Berstad. Thus, the idea of combining HBsAg produced in *Pichia pastoris*, TT and DT for nasal administration flows logically from their having been individually taught in the prior art. The mucosal immunization of a combination of HBsAg with TT, DT and Hib for

their additive effects and more cost-effect efficient renders the invention *prima facie* obvious.

Response to Applicant's arguments:

15. Applicant argues that (1) Claim 1 has been amended to specify that *Bordatella pertusis* is whole cell, and the cited Schmitt reference teaches is acellular, not whole cell *Bordatella pertusis*. None of the other references cited by the examiner indicates the use of *Bordetella pertussis* either whole-cell or acellular.

16. In response, newly cited Berstad reference teaches a nasal *Bordetella pertussis* whole-cell antigen that can induce specific systemic and cross-reactive mucosal antibody responses in human, which shows that both the knowledge and the material of nasal *Bordetella pertussis* whole-cell vaccines were in possession of one of ordinary skill in the art at the time the instant invention was made. The reason and motivation to incorporate a nasal *Bordetella pertussis* whole-cell vaccine in the combination of vaccines as an alternative is set forth in Para 11 above.

17. Applicant argues that (2) EP 0864649A2 only teaches a single vaccine HBsAg produced by *Pichia pastoris*, no combination of vaccines is evaluated. The enhanced immunogenicity seen in the HBsAg produced by *Pichia pastoris* is not known to extended beyond to HBsAg to create an adjuvant effect on other vaccines co-administered.

18. Applicant's argument is considered but found not persuasive. Since the HBsAg produced by *Pichia pastoris* as a vaccine and its immunogenicity has been disclosed and taught by EP0864649, its inherent properties, such as its ability as an adjuvant effect on other vaccines co-administered, are also disclosed, even though the property was not recognized before.

Thus, Applicant has not presented compelling reasons to overcome the 103 rejection.

Remarks

19. No claim is allowed. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, Ph. D. can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

BP

Bo Peng, Ph.D.
October 29, 2007

Bruce Campell

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